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(54) **Title:** THIENO-INDOLE DERIVATIVES AS 5HT2c AND 5HT2b ANTAGONISTS

(57) **Abstract**

Novel thieno-indole compounds being 5HT2c and 5HT2b antagonists, processes for their preparation, compositions containing them and their use in the treatment of mammals.

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THIENO-INDOLE DERIVATIVES AS 5HT2c AND 5HT2b ANTAGONISTS

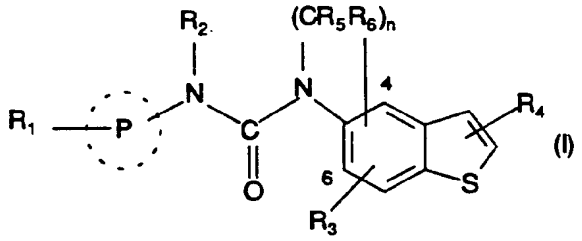
This invention relates to novel compounds having pharmacological activity, to processes for their preparation, to compositions containing them and to their use in the treatment of mammals.

P. Fludzinski **et. al.**, J. Med. Chem. 1986 **29** 2415-2418 describes N-(1,2-dimethyl-3-ethyl-1H-indol-5-yl)-N'- (3-trifluoromethylphenyl)urea which shows selectivity for the rat stomach fundus serotonin receptor.

WO 92/05170 describes certain urea derivatives which are described as possessing $5HT_{1C}$ receptor antagonist activity. The $5HT_{1C}$ receptor has recently been reclassified as the $5HT_{2C}$ receptor [P. Hartig **et al.**, Trends in Pharmacological Sciences (TIPS) 1993].

A structurally distinct class of compounds has now been discovered which have been found to have $5HT_{2C}$ receptor antagonist activity. Certain compounds of the invention also exhibit $5HT_{2B}$ antagonist activity. $5HT_{2C/2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Accordingly, the present invention provides a compound of formula (I) or a salt thereof:



(I)

wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R_1 is hydrogen, C_{1-6} alkyl, halogen, OR_7 or NR_8R_9 where R_7, R_8 and R_9 are

independently hydrogen or C_{1-6} alkyl;
R_2 is hydrogen or C_{1-6} alkyl;
R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;
R_4 is hydrogen or C_{1-6} alkyl;
R_5 and R_6 are each independently hydrogen or C_{1-6} alkyl; and
n is 2 or 3.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chained or branched and are preferably C_{1-3} alkyl, such as methyl, ethyl, **n**- and **iso**- propyl, most preferably methyl.

Preferably R_1 is hydrogen, C_{1-6}alkyl or halogen. Most preferably R_1 is hydrogen, methyl or bromo.

Preferably R_2 and R_3 are hydrogen.

Preferably R_5 and R_6 are both hydrogen and n is 2, that is to say, the group $-(CR_5R_6)_n-$ forms an ethylene linkage. The group $-(CR_5R_6)_n-$ can be attached to the 4- or 6-position of the benzothiophene ring.

The urea moiety can be attached to a carbon or, when available, a nitrogen atom of the ring P, preferably it is attached to a carbon atom.

Suitable moieties when the ring P is a 5- or 6-membered aromatic heterocyclic ring include pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. When P is a quinoline or isoquinoline residue, the urea moiety can be attached at any position of the ring, preferably to the 4-position.

Preferably P is pyridyl, quinolyl or isothiazolyl.

The substituent R_3 can be attached to any vacant position in the phenyl part of the benzothiophene ring, that is to say, the 4-, 6- or 7-positions of the benzene ring. The substituent R_4 can be attached to the 2- or 3-positions of the thiophene ring.

Preferred compounds of formula (I) include;
7,8-Dihydro-6-(3-pyridylcarbamoyl)-thieno[3,2-e]-indole,

6,7-Dihydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
7,8-Dihydro-6-(5-quinolylcarbamoyl)-6H-thieno[3,2-e]indole,
7,8-Dihydro-6-(3-Methyl-5-isothiazolylcarbamoyl)-6H-thieno[3,2-e]indole,
6,7-Dihydro-5-(5-Bromo-3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
7,8-Dihydro-6-(2-methyl-4-quinolylcarbamoyl)-6H-thieno[3,2-e]indole,
6,7-Dihydro-5-(2-methyl-4-quinolylcarbamoyl)-5H-thieno[2,3-f]indole,
6,7-Dihydro-5-(4-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
and pharmaceutically acceptable salts thereof.

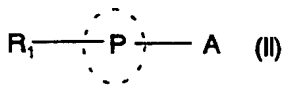
The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form N-oxides, S-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. When R_2 is hydrogen or when R_1 is hydroxy or NR_7R_8 and at least one of R_7 and R_8 are hydrogen, the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to all tautomeric forms of compounds of formula (I) and mixtures thereof.

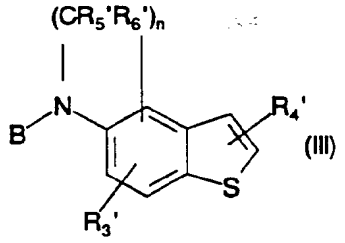
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II);



(II)

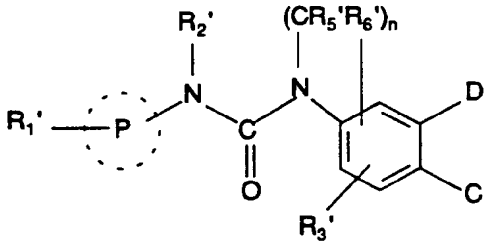
with a compound of formula (III);



(III)

wherein A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_2'CO$ when coupled, wherein R_2' is R_2 as defined in formula (I) or a group convertible thereto, and the variables R_1', R_3', R_4', R_5' and R_6' are R_1, R_3, R_4, R_5 and R_6, respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5' and R_6' when other than R_1, R_2, R_3, R_4, R_5 and R_6 to R_1, R_2, R_3, R_4, R_5 and R_6, interconverting R_1, R_2, R_3, R_4, R_5 and R_6, and forming a pharmaceutically acceptable salt, or

(b) cyclising a compound of formula (IV):



(IV)

wherein R_1', R_2', R_3', R_5', and R_6' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the thiophene ring substituted by R_3' and R_4' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5' and R_6' when other than R_1, R_2, R_3, R_4, R_5 and R_6 to R_1, R_2, R_3, R_4, R_5 and R_6, interconverting R_1, R_2, R_3, R_4, R_5 and R_6, and forming a pharmaceutically acceptable salt.

Suitable examples of groups A and B include:

(i) A is -N=C=O and B is -H,

(ii) A is $-NR_2'COL$ and B is -H,

(iii) A is $-NHR_2'$ and B is COL, or

(iv) A is halogen and B is $-CONHR_2'$,

wherein R_2' is as defined above and L is a leaving group. Examples of suitable leaving

groups L include imidazole, halogen such as chloro or bromo or phenoxy or phenylthio optionally substituted, for example with halogen.

When A is -N=C=O and B is H the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is $-NR_2'COL$ and B is H or when A is $-NHR_2'$ and B is COL, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and B is $CONHR_2'$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

Examples of compounds of formula (IV) which can be used in the preparation of benzothiophenes include those where C is $SCH_2CO_2R_5$ where R_5 is C_{1-6} alkyl and D is CHO, or C is $SCH_2CH(OR_5)_2$ and D is hydrogen.

Suitable examples of groups R_1', R_3' and R_4' groups which are convertible to R_1, R_3 and R_4 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R_1 is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyloxy which is cleaved by hydrogenation. Suitable examples of a group R_2' which is convertible to R_2 include alkoxycarbonyl and benzyl or **para**-methoxybenzyl which are converted to R_2 is hydrogen using conventional conditions.

Interconversions of R_1, R_2, R_3 and R_4 are carried out by conventional procedures. For example, in the case where R_2 is hydrogen it is possible to introduce a C_{1-6} alkyl group at the R_2 position by conventional alkylation using 1 molar equivalent of a C_{1-6} alkyl halide and 1 molar equivalent of a suitable base in an inert solvent.

It should be appreciated that it may be necessary to protect any R_1 to R_4 hydrogen variables which are not required to be interconverted. Suitable protecting groups and

methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981). It is preferable, however, to introduce and interconvert the groups R_1 to R_4 before coupling compounds of formulae (II) and (III) together, or cyclising the compound of formula (IV).

Compounds of formula (II) in which A is NHR_2' are known compounds or can be prepared analogously to known compounds, see, for example, WO 92/05170.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

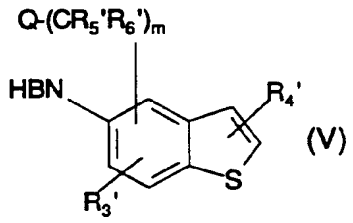
i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.
ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov **et al**, Helv. Chim. Acta 1987 **70** 262).
iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Examples of phosgene equivalents include carbonyldiimidazole and phenyl chloroformate.

Compounds of formula (II) in which A is $-NR_2'COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR_2'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) may be prepared:

(a) by cyclisation of compounds of formula (V), followed by reduction to the amine if necessary

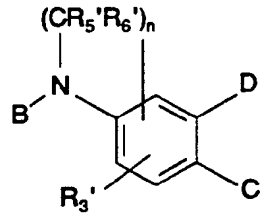


(V)

wherein Q is CR^5R^6L, CR^5O or CO_2R where L is a leaving group and R^5 and R^6 are as

defined in formula (I), m is 1 or 2, R_3', R_4', R_5', R_6' and B are as defined in relation to formula (III) above and R is aryl or alkyl group,

or (b) cyclisation of compounds of formula (VI)



(VI)

wherein R_3', R_5', R_6' and B are as defined in relation to formula (III) above and C and D are as defined in relation to formula (IV) above.

The cyclisation of a compound of formula (V) may be suitably carried out in an inert solvent at ambient or elevated temperatures, optionally in the presence of a base. Reduction, if necessary, may be carried out using conventional reduction techniques. The cyclisation of a compound of formula (VI) may be suitably carried out using the procedures outlined for the cyclisation of a compound of formula (IV), above.

Compounds of formula (II) in which A is halogen and B is hydrogen are commercially available. Novel intermediates of formulae (III) and (IV) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2C/2B}$ receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders,

Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

The invention further provides a method of treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

The following examples illustrate the invention.

Description 1
5-Nitrobenzo[b]thiophene (D1)

Ethyl 5-nitrobenzo[b]thiophenecarboxylate was prepared and hydrolysed to the corresponding acid as described by S. Rossi and R. Trave (Il Farmaco - Ed. Sci., 1960, **15**, 396). 5-Nitrobenzo[b]thiophenecarboxylic acid (4.32 g, 19.4 mmol) was heated with copper powder (1.2 g, activated by heating for several hours at 160°C **in vacuo**) in quinoline (25 ml) at 180-190°C for 2h. After cooling, the mixture was diluted with ether and washed thoroughly with 5N hydrochloric acid. The organic phase was dried and evaporated, and the crude product was recrystallised from ether to give the title compound (3.24 g, 77%), m.p. 142-145°C.

NMR ($CDCl_3$) δ: 7.52 (1H, d, J 6), 7.68 (1H, d, J 6), 8.00 (1H, d, J 8), 8.22 (1H, dd, J 8, 2), 8.74 (1H, d, J 2).

Description 2
4-Methyl-5-nitrobenzo[b]thiophene(D2)

To a solution of 5-nitrobenzo[b]thiophene(D1) (1.79g, 10 mmol) in dry THF (100 ml), cooled to -20° C, was added methylmagnesium bromide (3M in ether, 6.66 ml, 20 mmol), such that internal temperature remained below -15° C. The mixture was then stirred at this temperature for 30 min. 2, 3-Dichloro-5,6-dicyanobenzoquinone (2.72 g, 12 mmol) was added and the mixture was stirred for 15 min. at room temperature. The mixture was then poured into dilute acetic acid (aqueous) and extracted three times with dichloromethane. Extracts were combined, washed with sodium bicarbonate (twice) and water, dried and evaporated. The residue was chromatographed on silica gel (120g) eluted with 1:1 petrol/dichloromethane to give the title compound (1.35 g; 47% combined yield from two preparations), m.p. 104-105° C (ether/petrol).

NMR ($CDCl_3$)δ: 2.88 (3H, s), 7.60 (1H, d, J=6), 7.64 (1H, d, J=6), 7.81 (1H, d, J=10), 7.92 (1H, d, J=10)

Description 3
4-(2-Hydroxyethyl)-5-nitrobenzo[b]thiophene (D3)

A mixture of 4-methyl-5-nitrobenzothiophene (D2) (1.045 g, 5.5 mmol), paraformaldehyde (0.18 g, 6 mmol) and potassium hydroxide (0.5 M in ethanol, 1.2 ml, 0.6 mmol) in DMSO (10 ml) was stirred at room temperature for 4 h. The mixture was then diluted with ethyl acetate and washed thoroughly with water. The organic phase was dried and evaporated, and the residue was chromatographed on silica gel (60g) eluted with 0-1.5% methanol/dichloromethane, to give the title compound (0.92 g, 75%), m.p. 83-85°

NMR ($CDCl_3$)δ: 1.82 (1H, t, J=6), 3.51 (2H, t, J=6), 4.08 (2H, q, J=6), 7.66 (2H, s), 7.84 (1H, d, J=10). 7.91 (1H, d, J=10)

Description 4
4-(2-Methylsulphonyloxyethyl)-5-nitrobenzo[b]thiophene(D4)

A mixture of hydroxyethyl compound (D3) (1.03g, 4.6 mmol), methylsulphonyl chloride (0.4 ml, 5.2 mmol) and triethylamine (0.7 ml, 5 mmol) in dichloromethane (20 ml) was stirred for 1 h at room temperature. A further portion of triethylamine (0.2 ml) was added and stirring was continued for 30 min. Water (10 ml) was then added and the mixture was stirred for approx. 10 min before acidification with 5M hydrochloric acid and separation of phases. The organic phase was washed with dilute hydrochloric acid, dried and evaporated. The residue was recrystallised from ether to give the title compound (1.0 g, 72%), m.p. 108-110° C.

NMR ($CDCl_3$)δ: 2.97 (3H, s), 3.72 (2H, t, J=6), 4.67 (2H, t, J=6), 7.71 (1H, d, J=6), 7.74 (1H, d, J=6), 7.92 (1H, d, J=10), 7.99 (1H, d, J=10)

Description 5
7,8-Dihydrothieno[3,2-e]indole (D5)

A mixture of the methanesulphonate (D4) (1.0g, 3.3mmol) and 10% palladium on charcoal (0.1 g) in ethanol (50 ml) was stirred under hydrogen at 47 psi for 6.5 h. A further 50 mg of palladium/charcoal was added and hydrogenation continued for 7 h. The mixture was filtered through kieselguhr and evaporated. The residue was partitioned between dichloromethane and water and the organic phase was extracted with dilute hydrochloric acid. The combined aqueous extracts were basified with 10% sodium hydroxide and extracted with DCM. The organic extract was dried and evaporated to give the title compound (0.18 g, 31%) as a greenish oil.

NMR ($CDCl_3$)δ: 3.31 (2H, t, J=8), 3.78 (2H, t, J=8), 4.75 (broad s), 6.96 (1H, d, J=10), 7.18 (1H, d, J=6), 7.48 (1H, d, J=6), 7.60 (1H, d, J=10)

Description 6

***2-Bromo-4-methylbenzenecarboxaldehyde (D6)**

Sodium nitrite (45.0g, 650 mmoles) in water (80 ml) was added dropwise to a mixture of 2-bromo-4-methylaniline (100.0g, 530 mmoles), concentrated hydrochloric acid (125 ml) and ice/water (400 ml) over 30 mins keeping the temperature <5° C. The mixture was stirred for a further 30 mins at 0° C and sodium acetate trihydrate (50.0g, 360 mmoles) was added.

The diazonium solution/suspension was then added portionwise via a transfer tube to a solution of formaldoxime [formaldoxime prepared from paraformaldehyde (32.5g, 1000 mmoles) and hydroxylamine hydrochloride (74.0g, 1050 mmoles) by heating under reflux in water (400 ml) with sodium acetate trihydrate (150.0g, 1080 mmoles), copper sulphate pentahydrate (16.3g), sodium sulphite (2.2g) and anhydrous sodium acetate (210g, 2560 mmoles) for 20 mins] with vigorous stirring keeping the temperature <15° C (Care! reaction froths greatly). The mixture was stirred at ambient temperature for 1 hr and concentrated hydrochloric acid (470ml) was added. The mixture was then heated under reflux for 1 hr.

The product was steam distilled from the reaction for 3 hr and then extracted into diethyl ether (2x1000 ml), washed with saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to dryness. Vacuum distillation at 5 mm Hg gave the title compound (57g, 53%) b.p. 102-108° C

NMR ($CDCl_3$) δ : 2.41 (3H, s), 7.22 (1H, d, J 8), 7.48 (1H, s), 7.81 (1H, d, J 8), 10.30 (1H, s).

* S.D. Jolad, S. Rajagopal, Org Synth Coll Vol, V, P.139, (1973)

Description 7

2-Bromo-4-methyl-5-nitrobenzenecarboxaldehyde (D7)

Concentrated nitric acid (36ml, 570 mmoles) was added dropwise to 2-bromo-4-methylbenzene-carboxaldehyde (D6) (57g, 285 mmoles) in concentrated sulphuric acid (300 ml) with stirring keeping the temperature <15° C. The mixture was stirred for a further 20 mins then poured onto ice/water (250 ml) with vigorous stirring. The mixture was extracted with 5% methanol/chloroform (3 x 1000 ml), washed with saturated sodium bicarbonate solution, filtered and evaporated to dryness. The residue was recrystallised from ethyl acetate/60-80 petrol to give the title compound (44.2g, 63%).

NMR ($CDCl_3$) δ : 2.63 (3H, s), 7.68 (1H, s), 8.49 (1H, s), 10.30 (1H, s).

Description 8

Ethyl-5-nitro-6-methylbenzo[b]thiophene-2-carboxylate (D8)

Ethyl-2-mercaptoacetate (20 ml, 182 mmoles) was added to a solution of sodium ethoxide [prepared by treating ethanol (150 ml) with sodium metal (4.3g, 180 mmoles)] keeping the temperature <5° C. After 20 mins ethanol (300 ml) was added followed by 2-bromo-4-methyl-5-nitrobenzene-carboxaldehyde (D7) (44.2g, 180 mmoles) portionwise over 10 mins resulting in a dense yellow precipitate. More ethanol (200 ml) was added and the mixture heated under reflux for 3 hr. The mixture was allowed to cool and the ethanol was removed *in vacuo*. The residue was partitioned between dichloromethane and water, separated, dried (Na_2SO_4) and evaporated to dryness to give the title compound (46.0g, 96%).

NMR ($CDCl_3$) δ : 1.42 (3H, t, J 6), 2.72 (3H, s), 4.42 (2H, q, J 6), 7.80 (1H, s), 8.10 (1H, s), 8.53 (1H, s).

Description 9

5-Nitro-6-methylbenzo[b]thiophene (D9)

Ethyl-5-nitro-6-methylbenzo[b]thiophene-2-carboxylate (D8) (46.0g, 170 mmoles) in ethanol (500 ml) and water (300 ml) was heated under reflux with sodium hydroxide (27.0 g, 680 mmoles) for 3 hours. The mixture was then allowed to cool and most of the ethanol was removed *in vacuo*. The aqueous was then poured into a mixture of dilute hydrochloric acid (250 ml) and ice/water (100 ml) with vigorous stirring. The resulting fine precipitate was filtered off and dried. The dry solid was then heated in quinoline (300 ml) with copper powder (25 g, 390 mmoles) to 190° C for 3 hrs with stirring. The mixture

was then cooled and diluted with diethyl ether (100 ml), filtered through kieselguhr. The filtrate was washed with dilute hydrochloric acid (3 x 500 ml), water (500 ml) and saturated sodium chloride (500 ml), separated, dried (Na_2SO_4), filtered and evaporated to dryness to give the title compound (29.6g, 88%)

NMR ($CDCl_3$) δ : 2.70 (3H, s), 7.40 (1H, d, J 6), 7.55 (1H, d, J 6), 7.80 (1H, s), 8.49 (1H, s).

Description 10

2-(5-Nitro-6-benzo[b]thienyl)acetaldehyde (D10)

5-Nitro-6-methylbenzo[b]thiophene (D9) (29.6g, 153 mmoles) in dimethyl formamide (300 ml) was treated with dimethylformamide dimethyl acetal (61 ml, 460 mmoles) and pyrrolidine (25.7 ml, 300 mmoles) and heated to 150° C for 3 hrs under argon. The mixture was then cooled and evaporated to dryness. Toluene (600 ml), water (800 ml) and dilute hydrochloric acid (300 ml) were added to the residue and the mixture heated under reflux for 30 mins. The mixture was cooled and extracted with ethyl acetate (2 x 600 ml). The organic layer was washed with water (500 ml), dried (Na_2SO_4) and evaporated to dryness. Flash chromatography on TLC silica gel eluting with dichloromethane gave the title compound (26.4g, 78%)

NMR ($CDCl_3$) δ : 4.21 (2H, s), 7.48 (1H, d, J 6), 7.63 (1H, d, J 6), 7.79 (1H, s), 8.63 (1H, s), 9.90 (1H, s)

Description 11

2-(5-Nitro-6-benzo[b]thienyl)ethanol (D11)

2-(5-Nitro-6-benzo[b]thienyl)acetaldehyde (D10) (25.3g, 114 mmoles) in ethanol was treated with sodium borohydride (8.7g, 228 mmoles) with stirring at ambient temperature. Stirring was continued for 1 hr then most of the ethanol was removed *in vacuo*. Water (500 ml) was added. The mixture was then acidified by careful addition of dilute hydrochloric acid (gas evolution) and then extracted with ethyl acetate (2 x 400 ml). The combined organics were washed with water (500 ml) and saturated sodium chloride solution (500 ml), separated, dried (Na_2SO_4) and evaporated to dryness. This gave the title compound (25.0g, 98%).

NMR ($CDCl_3$) δ : 3.28 (2H, t, J 8), 3.95 (2H, t, J 8), 7.40 (1H, d, J 6), 7.58 (1H, d, J 6), 7.89 (1H, s), 8.45 (1H, s).

Description 12

2-(5-Nitro-6-benzo[b]thienyl)ethyl methane sulphonate (D12)

2-(5-Nitro-6-benzo[b]thienyl)ethanol (D11) (25.0 g, 112 mmoles) in dichloromethane (500 ml) was treated with triethylamine (16.4 ml, 118 mmoles). Methanesulphonyl chloride (9.2 ml, 118 mmoles) was then added dropwise with stirring over 15 mins. The mixture was stirred for a further 1 hr then washed with saturated aqueous sodium bicarbonate (2 x 500 ml), dried (Na_2, SO_4) and evaporated to dryness to give the title compound (19.6g, 88%).

NMR ($CDCl_3$) δ : 2.98 (3H, s), 3.45 (2H, d, J 8), 4.60 (2H, d, J 8), 7.45 (1H, d, J 6), 7.63 (1H, d, J 6), 7.89 (1H, s), 8.51 (1H, s)

Description 13

6,7-Dihydro-5H-thieno[2,3-f]indole (D13)

The methanesulphonate (D12) (24.0g, 80 mmoles) was hydrogenated at atmospheric pressure and at 50° C for 3 hrs in ethyl acetate (600 ml) with triethylamine (40 ml) over a 10% palladium on charcoal catalyst. The catalyst was then filtered off and the filtrate washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4) and evaporated to dryness to give the title compound as an off-white solid (12.7g, 91%)

NMR ($CDCl_3$) δ : 3.12 (2H, t, J 8), 3.40-3.60 (1H, br s), 3.65 (2H, t, J 8), 7.01 (1H, s), 7.11 (1H, d, J 6), 7.25 (1H, d, J 6), 7.53 (1H, s)

Example 1

7,8-Dihydro-6-(3-pyridylcarbamoyl)-thieno[3,2-e]-indole (E1)

A solution of nicotinic acid azide (0.16 g, 1.1 mmol) in toluene (7 ml) was heated under reflux for 1.5 h. The solution was cooled and thienoindole (D5) (0.18g, 1.03 mmol) was added in dichloromethane (7 ml) containing a little dimethylformamide. The mixture was stirred at room temperature for 2.5 h. The mixture was then washed with water, and the aqueous phase was extracted with dichloromethane/methanol. The toluene phase and the dichloromethane extract were combined, dried and evaporated. The residue was

recrystallised from ethanol/water to give the title compound (0.18 g, 59%) m.p. 192-197° C.

Found: C, 64.97; H, 4.63; N, 14.05%
$C_{16}H_{13}N_3OS$ requires: C, 65.06; H, 4.44; N, 14.23%

NMR(D_6-DMSO)δ: 3.45(2H, t, J=8), 4.30 (2H, t, J=8), 7.33 (1H, d, J=6), 7.36 (1H, d, J=6), 7.78 (1H, d, J=6), 7.80 (1H, d, J=6), 8.01 (1H, m, J=7), 8.07 (1H, d, J=7), 8.24 (1H, d, J=4), 8.74 (1H, s), 8.78 (1H, s)

Example 2
6,7-Dihydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole (E2)

Nicotinyl azide (0.06g, 0.4 mmol) in toluene (3ml) was heated under reflux for 1 h, then cooled. 6,7-Dihydro-5H-thieno[2,3-f]indole (0.07g, 0.4 mmol) in dichloro- methane was added and the mixture was stirred for 1 h at room temperature. A little petrol was added and the solid product was filtered off, washed with petrol and dried *in vacuo* to give the title compound (0.085g, 72%), m.p. 183-185° C.

Found: C, 64.94; H, 4.73; N, 14.26 %
$C_{16}H_{13}N_3OS$ requires C, 65.06; H, 4.44; N, 14.23%

NMR (D_6-DMSO) d: 3.28 (2H, t, J=9), 4.22 (2H, t, J=9), 7.34 (1H, m), 7.37 (1H, d, J=5), 7.63 (1H, d, J=5), 7.77 (1H, s), 8.01 (1H, d, J=8), 8.23 (1H, d, J=5), 8.33 (1H, s), 8.75 (2H, m).

Example 3
7,8-Dihydro-6-(5-quinolylcarbamoyl)-6H-thieno[3,2-e]indole (E3)

5-Aminoquinoline (0.27g, 1.9 mmol) and 1,1'-carbonyldiimidazole (0.31g, 1.9 mmol) were stirred at reflux under Ar in dry dichloromethane (10 ml) for 2.5h. The mixture was evaporated to dryness, and the residue was dissolved in dry DMF (10 ml). 7,8-Dihydro-6H-thieno[3,2-e]indole (D5) (0.30g, 1.7 mmol) was added, and this mixture was stirred at 115° C for 1h, when it was poured into water (200 ml). The precipitate was filtered off and dried *in vacuo*. Chromatography on silica gel, eluting with 0-1% methanol/ethyl acetate, gave the title compound (0.31g, 52%) as a greenish-grey powder, m.p. 243-4° C.

NMR ($DMSOd_6$) (δ): 3.49 (2H, t, J 8), 4.44 (2H, t, J 8), 7.36 (1H, d, J 5), 7.53 (1H, dd, J 8, 4), 7.64 (1H, d, J 7), 7.7-7.85 (3H, m), 7.92 (1H, d, J 8), 8.03 (1H, d, J 9), 8.48 (1H, d, J 8), 8.85 (1H, s), 8.92 (1H, m)

Found: C, 66.7; H, 4.4; N, 11.7%
$C_{20}H_{15}N_3OS$ $0.75H_2O$ requires C, 66.9; H, 4.6; N, 11.7%

Example 4

7,8-Dihydro-6-(3-Methyl-5-isothiazolylcarbamoyl)-6H-thieno[3,2-e]indole (E4)

This was prepared from 5-amino-3-methylisothiazole hydrochloride (0.26g, 1.7mmol) and 7,8-dihydro-6H-thieno[3,2-e]indole (D5), following the procedure of Example 3, but including 1 equivalent of triethylamine in the initial step. Recrystallisation from methanol/dichloromethane gave the desired material.

NMR ($DMSOd_6$) (δ): 2.30 (3H, s), 3.47 (2H, t, J 8), 4.26 (2H, t, J 8), 6.77 (1H, s), 7.36 (1H, d, J 6), 7.8 (2H, m), 8.06 (1H, d, J 8), 10.55 (1H, b s).

Found: C, 57.1; H, 4.3; N, 13.4%. $C_{15}H_{13}NOS_2$ requires C, 57.1; H, 4.2; N, 13.3%

Example 5

6,7-Dihydro-5-(5-Bromo-3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole (E5)

This was prepared from 6,7-dihydro-5H-thieno[2,3-f]indole (D) (0.28g, 1.6 mmol) and 5-bromonicotinoyl azide (0.38g, 1.7 mmol), following the procedure of Example 2. Recrystallisation of the crude product from ethanol/petroleum ether (b.p. 60-80°C) gave the title compound (0.16g, 34%) as an off-white solid, m.p. 203-5° C decomp.

NMR ($DMSOd_6$) (δ): 3.34 (2H, t, J 8), 4.23 (2H, t, J 8), 7.39 (1H, d, J 4), 7.65 (1H, d, J 4), 7.80 (1H, s), 8.35 (3H, m), 8.78 (1H, d, J 2), 8.97 (1H, s)

Found: C, 51.2; H, 3.4; N, 11.0%. $C_{16}H_{12}BrN_3OS$ requires: C, 51.4; H, 3.2; N, 11.2%

Example 6

7,8-Dihydro-6-(2-methyl-4-quinolylcarbamoyl)-6H-thieno[3,2-e]indole (E6)

To an ice-cooled solution of 1,1'-carbonyl diimidazole (0.47g, 2.86 mmol) in dry

dichloromethane (15 ml) was added 4-aminoquinaldine (0.41g, 2.6 mmol) in dichloromethane (30 ml). The mixture was stirred for 1.75 h while warming from 0°C to room temperature. Solvent was then evaporated and replaced by dry DMF (10 ml). A solution of 7,8-dihydro-6H-thieno[3,2-e]indole (D5, 0.45g, 2.57 mmol) in dry DMF (10 ml) was added, and the mixture was stirred for 1.25h at 100-120° C. The mixture was then cooled and poured into water. The solid product was filtered off, washed with water and dried, then recrystallised twice from dichloromethane/petrol to give the title compound (0.35g, 38%), m.p. 229-231° C.

NMR (DMSOd_6) (δ): 2.65 (3H, s), 3.49 (2H, t, J 8), 4.50 (2H, t, J 8), 7.38 (1H, d, J 6), 7.54 (1H, t, J 7), 7.72 (1H, t, J 7), 7.80 (3H, m), 7.92 (1H, d, J 7), 8.07 (1H, d, J 7), 8.18 (1H, d, J 7), 8.87 (1H, s)

Found: C, 70.04; H, 5.02; N, 11.66%
$C_{21}H_{17}N_3OS$ requires C, 70.17; H, 4.77; N, 11.69%

Example 7
6,7-Dihydro-5-(2-methyl-4-quinolylcarbamoyl)-5H-thieno[2,3-f]indole (E7)

The title compound was prepared by the method of Example 3 from 2-methyl-4-aminoquinoline (0.46g, 29 mmoles) and 6,7-dihydro-5H-thieno [2,3-f] indole (D13) (0.5g, 29 mmoles). Recrystallisation from methanol/dichloromethane gave the title compound as white crystals (0.51g, 49%) m.p. 237-8° C.

NMR (DMSO-d_6) δ : 2.60 (3H, s), 3.30 (2H, t, J 8), 4.40 (2H, t, J 8), 7.35 (1H, d, J 6), 7.45-7.55 (1H, m), 7.60-7.95 (5H, m), 8.10-8.21 (1H, m), 8.35 (1H, s), 8.30-8.45 (1H, brs).

Found: C, 69.87; H, 4.89; N, 11.70%
$C_{21}H_{17}N_3OS$ requires: C, 70.17; H, 4.77; N, 11.69%
Found M^+, $C_{21}H_{17}N_3OS$ requires 359

Example 8
6,7-Dihydro-5-(4-pyridylcarbamoyl)-5H-thieno[2,3-f]indole (E8)

The title compound was prepared by the method of Example 3 from 4-aminopyridine

(0.27g, 29 mmoles) and 6,7-dihydro-5H-thieno[2,3-f]indole (0.5g, 29 mmoles). Recrystallisation from methanol/dichloromethane gave the title compound as light green crystals (0.45g, 53%) m.p. >240° C.

NMR (DMSO-d_6) δ : 3.30 (2H, t, J 8), 4.22 (2H, t, J 8), 7.39 (1H, d, J 6), 7.59-7.68 (3H, m), 7.80 (1H, s), 8.30-8.44 (3H, m), 8.95 (1H, s).

Found: C, 63.91; H, 4.63; N, 14.10%

$C_{16}H_{13}N_3OS^1/_3H_2O$ requires: C, 63.79; H, 4.54; N, 13.95%

Found M^+ 295, $C_{16}H_{13}N_3OS$ requires 295

Pharmacological Data

Reversal of MCPP-induced Hypolocomotion

Administration of m-(chlorophenyl)piperazine (mCPP) to rats induces hypolocomotion (Kennett and Curzon 1988, Luckie *et al.* 1989) as seen with the related drug 1-(m-trifluoromethylphenyl)piperazine (TFMPP) (Lucki and Frazer 1982, Kennett and Curzon 1988). This effect was blocked by the non specific 5-HT_{2C}/5-HT_{2A} receptor antagonists mianserin, cyproheptadine and metergoline and perhaps by mesulergine. It was not blocked by the 5-HT_{2A} receptor antagonists ketanserin and ritanserin at relevant doses (Kennett and Curzon 1991) nor by antagonists of 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, α_2 adrenoceptors or dopamine D_2 receptors. The effect of mCPP is therefore considered to be mediated by 5-HT_{2C} receptors (Kennett and Curzon 1988) as confirmed by subsequent studies (Lucki *et al.*, 1989). Since mCPP causes hypolocomotion when infused into the cerebral ventricles this effect is probably centrally mediated (Kennett and Curzon 1988).

mCPP-induced hypolocomotion was measured in automated locomotion cages of dimensions 56 cm long x 16½ cm wide x 25 cm high and made of black perspex. Two photobeams traversed the width of the cages at either end at ground level. Sequential breaking of these beams allowed the measurement of cage transits.

Male Sprague Dawley rats (200-250g) (Charles River) were housed in groups of six. They were given drugs orally 1h pretest and 40 mins later mCPP (7 mg/kg i.p.). After a further 20 min they were placed in individual automated cages in groups of four under red light in an adjacent room. After 10 min the test was terminated. Reversal of mCPP-induced hypolocomotion was considered as evidence of *in vivo* central 5-HT_{2C} receptor antagonist properties.

Kennett, G.A., Curzon, G., (1988). Brit. J. Pharmacol. **94**, 137-147.
Kennet G.A., Curzon, G., (1991). Brit.J. Pharmacol. **103**, 2016-2020.
Lucki, I., Frazer, A., (1982) Am. Soc. Neurosci. 8(abstr.), 101.
Lucki, I., Ward, M.R., Frazer, A., (1989). J.Pharmacol. Exp. Therap. **249**, 155-164.

The compounds of examples 1, 2 and 5 had ID50 values of 1.4 to 9.6 mg/kg p.o.

[^{3}H]-mesulergine binding to rat or human 5-HT$_{2C}$ clones expressed in 293 cells in vitro

Evidence from the literature suggests that 5-HT$_{2C}$ antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT$_{2C}$ binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine from 5-HT$_{2C}$ clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos et al, 1984.

The cells suspension (50ml) was incubated with [^{3}H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10^{-6}M). Ten concentrations of test drug (3×10^{-9} to 10^{-4}M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC$_{50}$ values were determined using a four parameter logistic program (DeLean 1978) and the pK$_i$ (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

K$_i$ = inhibition constant.
C = concentration of [^{3}H]-mesulergine
Kd = Affinity of mesulergine for 5-HT$_{2C}$ binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.
Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.
Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

Julius *et al.* (1988) Science 241, 558-564
DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

The compounds of examples 1 to 8 had pK_i values from 5·1 to 8·4.

Geller-Seifter Procedure

Potential anxiolytic properties are evaluated using the Geller-Seifter procedure based on that originally described by Geller and Seifter, (1960) Psychopharmacologia, 1, 482-492. This procedure has been shown to be selective for drugs with anxiolytic properties (Cook and Sepinwall, (1975) "Mechanism of Action of Benzodiazepines" ed. Costa, E. and Greengard, P., Raven Press, New York, pp. 1-28).

Rats are trained on a variable interval 30 sec schedule (VI30) to press a lever in order to obtain food reward. The 5 min sessions of the VI30 schedule alternate with 2-5 min of a schedule (FR5) in which every 5th lever press is followed by presentation of a food pellet paired with a 0.5 sec mild footshock. The total study lasts approximately 30 mins. Rats typically respond with high rates of lever pressing under the VI30 schedule and low response rates under the FR5 'conflict' session. Anxiolytic drugs increase the suppressed response rates of rats in a 'conflict' session.

Drugs are administered intraperitoneally or orally to groups of 3-8 rats 30 min before testing. The results are expressed as the percentage increase in the square root of the total number of lever presses in the FR5 'conflict' session. Square root transformation is necessary to normalise the data for statistical analysis using parametric methods.

The compounds of Examples 1 and 2 showed a significant increase in responding in the 'conflict' session at dose levels in the range 1 to 2 mg/kg p.o.

Rat Fundus: 5-HT_{2B} Receptors

The 5-HT receptor in the rat fundic strip (RFS) has been characterised as 5-HT_{2B}. Hence this tissue may be used to assess the 5-HT_{2B} antagonist properties of compounds.

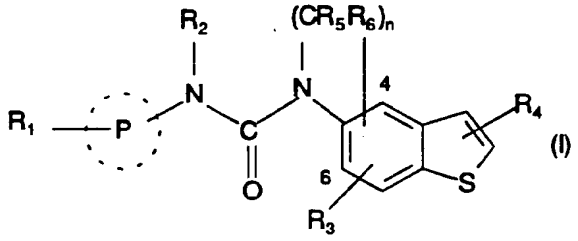
Whole stomachs were obtained from male CD Rats (Charles River, 250-350g). Strips of fundus (2cm x 0.5 cm) were cut from the greater curvature and the mucosae carefully

removed. Tissues were then further dissected into smaller strips (2mm x 20mm) which were mounted in organ baths containing oxygenated Tyrodes solution at 37° C containing indomethacin (3 μM). Preparations were maintained under a resting tension of 0.5g and exposed to the irreversible MAO inhibitor pargyline (100 μM for 30 minutes followed by washout). Over a 1h equilibration period, rat fundic strips were challenged with 1×10^{-8} M 5-HT at 15 minute intervals until cumulative concentration-effect curve to the standard agonist 5-HT (1×10^{-10} upwards) was constructed to determine the individual sensitivity of each preparation. A further concentration-effect curve to either 5-HT, or other agonists was constructed no sooner than 1h after completion of the previous curve. When necessary tissues were equilibrated with the antagonists over this one hour period. Antagonists affinities are expressed as pA_2 estimates.

The compound of Example 2 has a pA_2 value of 7.97.

Claims:

1. A compound of formula (I) or a salt thereof:



wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R_1 is hydrogen, C_{1-6} alkyl, halogen, OR_7 or NR_8R_9 where R_7, R_8 and R_9 are independently hydrogen or C_{1-6} alkyl;

R_2 is hydrogen or C_{1-6} alkyl;

R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

R_4 is hydrogen or C_{1-6} alkyl;

R_5 and R_6 are each independently hydrogen or C_{1-6} alkyl; and

n is 2 or 3.

2. A compound according to claim 1 in which R_1 is hydrogen, C_{1-6}alkyl or halogen.

3. A compound according to claim 1 or 2 in which R_2 and R_3 are hydrogen.

4. A compound according to any one of claims 1 to 3 in which R_5 and R_6 are both hydrogen and n is 2.

5. A compound according to any one of claims 1 to 4 in which P is pyridyl, quinolyl or isothiazolyl.

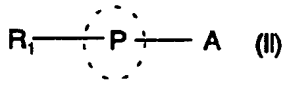
6. A compound according to claim 1 which is:

7,8-Dihydro-6-(3-pyridylcarbamoyl)-thieno[3,2-e]-indole,
6,7-Dihydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
7,8-Dihydro-6-(5-quinolylcarbamoyl)-6H-thieno[3,2-e]indole,
7,8-Dihydro-6-(3-Methyl-5-isothiazolylcarbamoyl)-6H-thieno[3,2-e]indole,
6,7-Dihydro-5-(5-Bromo-3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
7,8-Dihydro-6-(2-methyl-4-quinolylcarbamoyl)-6H-thieno[3,2-e]indole,
6,7-Dihydro-5-(2-methyl-4-quinolylcarbamoyl)-5H-thieno[2,3-f]indole,
6,7-Dihydro-5-(4-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
and pharmaceutically acceptable salts thereof.

7. A compound according to any one of claims 1 to 6 for use in therapy.

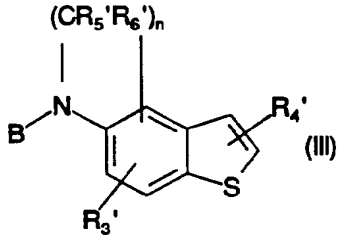
8. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

9. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:
(a) the coupling of a compound of formula (II);



(II)

with a compound of formula (III);

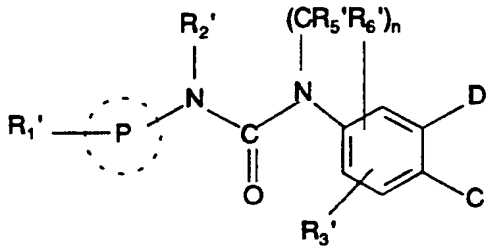


(III)

wherein A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_2'CO$ when coupled, wherein R_2' is R_2 as defined in formula (I) or a group convertible thereto, and the variables R_1', R_3', R_4', R_5' and R_6' are R_1, R_3, R_4, R_5 and R_6, respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5' and R_6' when other than R_1, R_2, R_3, R_4, R_5 and R_6 to R_1, R_2, R_3, R_4, R_5 and R_6,

interconverting R_1, R_2, R_3, R_4, R_5 and R_6, and forming a pharmaceutically acceptable salt, or

(b) cyclising a compound of formula (IV):



(IV)

wherein R_1', R_2', R_3', R_5', and R_6' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the thiophene ring substituted by R_3' and R_4' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1', R_2', R_3', R_4', R_5' and R_6' when other than R_1, R_2, R_3, R_4, R_5 and R_6 to R_1, R_2, R_3, R_4, R_5 and R_6, interconverting R_1, R_2, R_3, R_4, R_5 and R_6, and forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 94/00917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D495/04 A61K31/38 A61K31/17 //(C07D495/04,333:00, 209:00),(C07D495/04,333:00,221:00)

According to International Patent Classification (IPC) or to both nationa classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 05170 (SMITHKLINE BEECHAM PHARMACEUTICALS) 2 April 1992 cited in the application ---	1-9
P,A	WO,A,93 18028 (SMITHKLINE BEECHAM PHARMACEUTICALS) 16 September 1993 ---	1-9
P,X	WO,A,94 04533 (SMITHKLINE BEECHAM PHARMACEUTICALS) 3 March 1994 ---	1-9
A	J.MED.CHEM. vol. 29 , 1986 pages 2415 - 2418 FLUDZINSKI,P. ET AL. '2.3-Dialkyl(dimethylamino)indoles: Interaction with...' cited in the application -----	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1994	09. 08. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

In' ional Application No
PCT/EP 94/00917

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		AU-A-	8503891	15-04-92
		CA-A-	2091246	14-03-92
		EP-A-	0550507	14-07-93
		JP-T-	6500551	20-01-94
		US-A-	5328922	12-07-94
WO-A-9318028	16-09-93	NONE		
WO-A-9404533	03-03-94	AU-B-	4704693	15-03-94